Estimating the most efficient allocation of interventions to achieve reductions in *Plasmodium falciparum* malaria burden and transmission in Africa: a modelling study

Patrick G T Walker, Jamie T Griffin, Neil M Ferguson, Azra C Ghani

Summary

Background Reducing the burden of malaria is a global priority, but financial constraints mean that available resources must be allocated rationally to maximise their effect. We aimed to develop a model to estimate the most efficient (ie, minimum cost) ordering of interventions to reduce malaria burden and transmission. We also aimed to estimate the efficiency of different spatial scales of implementation.

Methods We combined a dynamic model capturing heterogeneity in malaria transmission across Africa with financial unit cost data for key malaria interventions. We combined estimates of patterns of malaria endemicity, seasonality in rainfall, and mosquito composition to map optimum packages of these interventions across Africa. Using non-linear optimisation methods, we examined how these optimum packages vary when control measures are deployed and assessed at national, subnational first administrative (provincial), or fine-scale (5 km² pixel) spatial scales.

Findings The most efficient package in a given setting varies depending on whether disease reduction or elimination is the target. Long-lasting insecticide-treated nets are generally the most cost-effective first intervention to achieve either goal, with seasonal malaria chemoprevention or indoor residual spraying added second depending on seasonality and vector species. These interventions are estimated to reduce malaria transmission to less than one case per 1000 people per year in 43·4% (95% CI 40·0–49·0) of the population at risk in Africa. Adding three rounds of mass drug administration per year is estimated to increase this proportion to 90·9% (95% CI 86·9–94·6). Further optimisation can be achieved by targeting policies at the provincial level, achieving an estimated 32·1% (95% CI 29·6–34·5) cost saving relative to adopting country-wide policies. Nevertheless, we predict that only 26 (95% CI 22–29) of 41 countries could reduce transmission to these levels with these approaches.

Interpretation These results highlight the cost–benefits of carefully tailoring malaria interventions to the ecological landscape of different areas. However, novel interventions are necessary if malaria eradication is to be achieved.

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Introduction

The 21st century has seen an unprecedented financial commitment towards reducing the burden of *Plasmodium falciparum* malaria.[1] Over the past decade, the proportion of the population of sub-Saharan Africa (the region with most global cases of malaria and deaths from the disease) with access to an insecticide-treated net has increased from 4% to 67% (95% CI 61–71) between 2004 and 2015, with an estimated 189 million long-lasting insecticide-treated nets delivered in 2014 alone.[2] This rapid scale-up in vector control has coincided with substantial improvements in access to prompt diagnosis and treatment using highly effective artemisinin combination therapies and chemoprevention within core risk groups, including young children and pregnant women.[3] These efforts have contributed to an estimated 26% reduction in the global incidence of clinical malaria and roughly 4·3 million deaths averted between 2000 and 2013.[3]

To date, with one exception (the recommendation of seasonal malaria chemoprevention),[4] universal coverage has been promoted—namely, all interventions are recommended in all settings. However, malaria transmission shows considerable variation at all spatial scales, ranging from hotspots within villages to differences between countries and continents.[5,6] Previous analyses have looked at how the cost-effectiveness of different combinations of interventions to reduce clinical disease and the morbidity associated with malaria vary according to different factors affecting transmission.[7–10] However, to date, no one has attempted to assess comprehensively how the optimum combinations of interventions to achieve malaria control targets vary across Africa as a result of such heterogeneity. In view of the current plateau in available funding for further malaria control and the subsequent shortfall in resources to achieve global goals,[1,3,11,12] there is a need to develop a rational basis to allocate the finite resources to achieve the greatest and most equitable effect.

To address this problem, we combined an existing malaria transmission model with estimates of the financial

Research in context

Evidence before this study

We searched PubMed with no date restriction for publications in English that combined models of malaria transmission with estimates of the resources needed to implement interventions, with the terms ("resource allocation" OR "optimal intervention" OR "cost minimisation" OR "cost effectiveness" OR "cost-effectiveness" OR "economic evaluation") AND ("model" OR "modelling") AND ("malaria" OR "falciparum" OR "plasmodium"). Our search yielded 147 results, 17 of which were judged relevant. Publications included various analyses of the cost-effectiveness of one or more malaria control interventions, sometimes taking into account ecological factors such as transmission intensity and vector behaviour and assessing how these affect the most cost-effective combination of interventions.

Added value of this study

To our knowledge, our study is the first that has attempted to estimate the optimum combination of interventions to achieve milestones for malaria burden and transmission reduction and to quantify how these packages are likely to vary across Africa. It is also the first study, to our knowledge, that looks at the extent to which the resources needed to achieve these targets can be reduced using control policies tailored to local ecology at the subnational first administrative (provincial) level.

Implications of all the available evidence

After universal coverage of long-lasting insecticide-treated nets, the optimum subsequent package of interventions differs depending on whether the target is a rapid reduction in malaria burden or sustained reductions in transmission. Nevertheless, currently recommended interventions are unlikely to achieve elimination in most malaria-endemic countries in Africa. New transmission-reducing interventions—eg, mass drug administration—could increase the number of countries in which elimination is feasible. For all policies, in countries with a high degree of heterogeneity in transmission, we find that interventions tailored to the provincial level are substantially more cost-efficient than are national policies. Moreover, these provincial-level policies typically capture most of the cost savings that could be obtained when attempting to achieve pre-elimination levels of transmission with finer spatial (5 km² pixel) stratification.

Panel: Summary of the model

We used an individual-based simulation model of the transmission dynamics and clinical burden of *Plasmodium falciparum* malaria, incorporating:

- Acquired immunity, which alters the likelihood that infection results in clinical disease, modifies onward infectivity to mosquitoes, affects the detectability of infection, and modifies the duration of parasitaemia
- Mosquito dynamics and behaviour relevant to control, including lifespan, density-dependent larval development, and feeding and resting behaviour
- Seasonality in larval carrying capacity informed by seasonal patterns in rainfall
- Characteristics of various first-line treatments for malaria, with profiles based on pharmacokinetic/pharmacodynamic (PK/PD) model fits to trial data
- A process-based model of the effect of vector control (long-lasting insecticide-treated nets [LLINs] and indoor residual spraying [IRS]), with parameters taken from detailed hut studies and fitted to intervention trial data
- Population-based, drug-based, intervention strategies, including seasonal malaria chemoprevention and mass drug administration, informed by PK/PD model fits to the individual drug properties and calibrated against trial data
- Realistic intervention variables, including attrition of LLINs due to wear and tear, waning of insecticides used within IRS or LLINs, and prespecified correlation between interventions and rounds of the same intervention

cost of different interventions to capture the non-linear dynamics of intervention effect and expenditure. We used this model to estimate the most cost-efficient strategies to achieve goals for reducing burden and transmission across a wide range of environments representative of areas in which the disease is currently prevalent in Africa.

Methods

Modelling specification and sampling framework

Using an individual-based mathematical model of *P falciparum* malaria transmission (panel),[13,14] we attempted to reflect the range of transmission settings across Africa, while maintaining a sampling framework that was computationally feasible. We simulated 288 baseline transmission settings comprising 18 transmission intensity strata (1% prevalence, then 5–85% prevalence in increments of 5%), four seasonality profiles, and four vector behaviours, ranging from mainly endophilic (indoor resting) and endophagic (indoor feeding) vectors, such as *Anopheles gambiae* sensu stricto or *Anopheles funestus*, to a vector with a lower human-biting index and higher propensity to feed and rest outdoors, such as *Anopheles arabiensis* (figure 1; appendix pp 2–8). For every setting, we simulated the effect of intervention packages over a 20-year time horizon, with all possible combinations of long-lasting insecticide-treated nets, indoor residual spraying, and seasonal malaria chemoprevention, ranging from 0% to 90% coverage in 15% increments. This simulation generated 98 784 scenarios.

We achieved scale-up of long-lasting insecticide-treated nets by providing a quarter of the total required nets for

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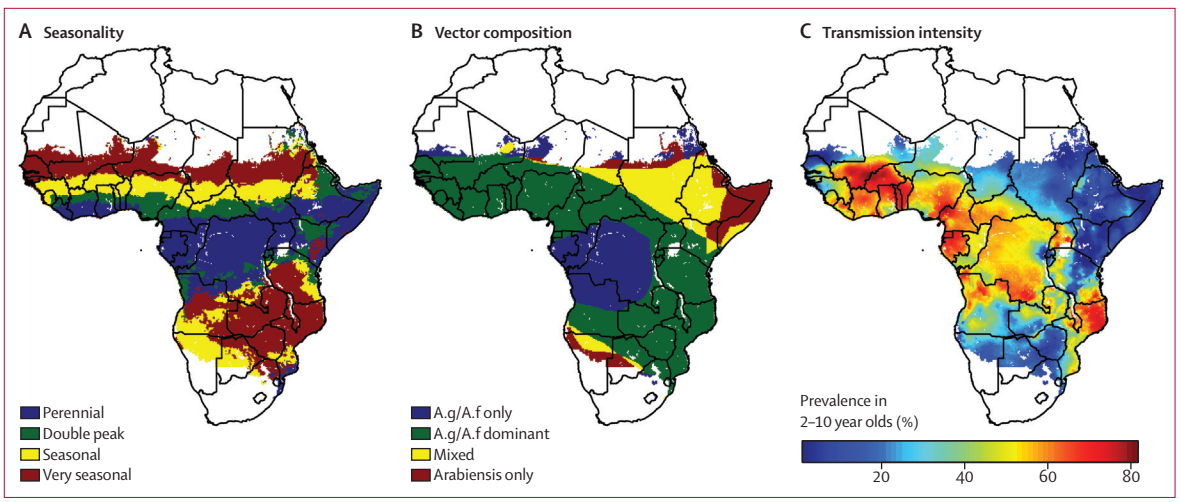

Figure 1: **Defining transmission settings across Africa**
(A) Distribution of the four seasonality templates based on rainfall patterns. (B) Vector species distribution for three key species groupings, based on presence and absence data.[15] A.g=*Anopheles gambiae* sensu stricto. A.f=*Anopheles funestus*. Arabiensis=*Anopheles arabiensis*. Mixed=all three species. (C) Estimates of malaria prevalence (blood film positivity) in children aged 2–10 years in 2000, back-calculated from estimates made for 2010,[6] using country-based estimates of scale-up for long-lasting insecticide-treated nets.

each of the first 4 years of roll-out and subsequently renewing these every 4 years, with killing and repellency fitted to hut trial data as described previously[14] and with a half-life of effectiveness of 2·64 years, reflecting a long-lasting insecticide.[16] We simulated indoor residual spraying with efficacy parameters based on a pirimiphos-methyl capsule-suspension compound (appendix pp 8–14), with killing and repellency parameters based on experimental hut trial data[17,18] and longevity based on cone assay data collated by the WHO Pesticide Evaluation Scheme (WHOPES).[19] We simulated seasonal malaria chemoprevention assuming that three monthly doses of sulfadoxine-pyrimethamine and amodiaquine were given to children aged 6–59 months;[4] we estimated the duration of prophylaxis from trial data,[20] with the timing of the second dose of sulfadoxine-pyrimethamine and amodiaquine calibrated to coincide with the annual peak in transmission. We simulated mass screen and treatment by using a rapid diagnostic test (assumed to have similar accuracy to microscopy)[21] and by providing dihydroartemisin-piperaquine (rINN, artenimol-piperaquine) to individuals with a positive result.[8] For mass drug administration, we assumed that all individuals received dihydroartemisin-piperaquine irrespective of infection status. We assumed 90% coverage and implementation of either one, two, or three rounds of mass drug administration per year, with rounds timed to maximise reduction in prevalence 5 years after implementation (appendix pp 14, 15).

When we looked at optimum packages to achieve pre-elimination status, we presumed that achieving robust surveillance would be a prerequisite, so we assumed 80% of clinical disease episodes received appropriate and effective artemisinin combination treatment in all scenarios. We also did a secondary analysis looking at optimum packages to reduce burden under the assumption that only 40% of cases received artemisinin combination treatment (appendix pp 19–23). For every intervention, we maintained coverage by redistributing the intervention to the same individuals within the population during every round. We assumed no correlation between the interventions an individual receives.

Resource calculation

We added the median unit procurement cost of a long-lasting insecticide-treated net (US$5·00 [IQR 4·50–6·60]), obtained from a review in west and central Africa,[22] to the median cost of delivering a net ($1·58), taken from a systematic review of costs.[23] We inflated these 2009 values to 2012 prices with a US$ inflation rate calculator to give a median cost per bednet distributed of $7·03 (IQR 6·51–8·24). For indoor residual spraying, we used the median cost per person per year protected of campaigns using pirimiphos-methyl, which we obtained from the President's Malaria Initiative Indoor Residual Spraying Country Programs,[24] giving a cost estimate of $8·80 per person per year in 2012. The cost in 2012 of three rounds of seasonal malaria chemoprevention per child using door-to-door delivery was estimated at $6·10 in Senegal[25] and $4·40 in Mali;[26] we used the average of these two estimates ($5·25). To reflect the fairly sparse data for costs of seasonal malaria chemoprevention and indoor residual spraying, compared with data for long-lasting insecticide-treated nets, we allowed the prices of these two interventions to vary between double and half these point estimates, according to a triangular distribution (table 1; appendix pp 16, 17).

For the non-drug costs of mass screen and treatment, we used a 2007 cost estimate of $5·08,[27] inflated to 2012 values. This estimate is based on the assumption that

For the **US$ inflation rate calculator** see http://www.usinflationcalculator.com/

	Estimate (US$, 2012)	Uncertainty distribution
Cost of distributing long-lasting insecticide-treated nets[22]	$7·03	Uniform (6·51–8·24)
Cost of indoor residual spraying (per person per year)[24]	$8·80	Triangle (4·40–17·60)
Cost of three rounds of seasonal malaria chemoprevention (per child per year)[25,26]	$5·25	Triangle (2·63–10·50)
Non-drug cost of mass screen and treatment (per person per round)[27]	$5·63	Not done*
Non-drug cost of mass drug administration (per person per round)[27]	$2·98	Triangle (1·49–5·96)
Full course of dihydroartemisin-piperaquine[8]	$1·65	Triangle (0·83–3·30)
Treatment of uncomplicated malaria with artemether-lumefantrine[8]	$2·50	Triangle (1·25–5·00)

*Uncertainty analysis was not done because we estimate that mass drug administration achieves the target in a substantially greater number of settings than does mass screen and treatment.

Table 1: **Unit costs for interventions**

the intervention uses community health workers already trained to manage fever presumptively and who are able to reach eight households per day. For the non-drug costs of mass drug administration, we assumed that remuneration, supervision, and training were 50% of the costs for mass screen and treatment, and we removed the unit costs of the rapid diagnostic test, lancet, and sterile gloves needed to provide diagnosis. This calculation resulted in a per-person non-drug cost of $2·98. Since the age profile of individuals with asymptomatic infection for mass screen and treatment, and that of the overall population for mass drug administration, is likely to be substantially older than the age distribution of those who typically have symptomatic malaria, we estimated an average cost of $1·65 for a curative course of dihydroartemisin-piperaquine, by taking into account the age structure of the population and age-dependent dosing recommendations.[8] For treatment of uncomplicated malaria, we assumed a cost of $2·50 per course, reflecting the cost of providing artemether-lumefantrine to a child after a positive rapid diagnostic test result.[8] To incorporate uncertainty in the cost of mass drug administration, we varied these costs between half and double their point estimates with a triangular distribution (table 1).

Mapping optimum intervention packages

We defined an optimum intervention combination for a given target as the combination that achieved this target at minimum cost. Across our 288 baseline settings, we compared the most efficient interventions to achieve either a 75% reduction in the burden of clinical disease from levels in 2000 (equivalent to the 2015 target within the Global Malaria Action Plan)[28] within a 5-year timeframe or a pre-elimination threshold of less than one case per 1000 population per year[29] at equilibrium (simulated over a 20-year timespan to avoid rebounds in incidence associated with this loss of immunity). We also did sensitivity analyses to assess the robustness of these estimated optimum packages to uncertainty in the model parameters determining the natural dynamics of infection and the effectiveness and costs of the three different interventions (appendix pp 19–23).

We divided Africa into $0·2° \times 0·2°$ (approximately 5 km²) pixels and matched every pixel to one of the 288 baseline settings, based on transmission intensity, seasonality, and vector bionomics, according to three metrics available at this resolution (figure 1). First, we used estimates of rainfall between 2002 and 2008,[30] smoothed by Fourier transform and matched to the four different seasonal patterns sampled using least squares estimation. Second, we based the presence and absence of the three vectors across Africa on estimates published by the Malaria Atlas Project.[31] Finally, we projected malaria prevalence (blood film positivity) in children aged 2–10 years in 2010 using data published by the Malaria Atlas project[6] and back-calculated to 2000 values with the model, calibrated to country-level estimates of insecticide-treated net scale-up and the appropriate vector and seasonality profile (appendix pp 15, 16).

We considered the optimum package to achieve our targets within every pixel; however, implementation or assessment of policies at such a local level is unlikely to be operationally feasible. Therefore, we also investigated the outcomes of optimising policies and monitoring outcomes at both the country level and the subnational first administrative (provincial) level. Throughout, we are forced to ignore local connectivity between pixels. To estimate the most efficient policy, we developed a stochastic simulated annealing algorithm (appendix pp 17–19).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Across all settings, long-lasting insecticide-treated nets were predicted to be the most resource-efficient intervention to reduce the burden of malaria disease (figure 2A). Nets alone were sufficient to reach our clinical incidence target in settings with baseline parasite prevalence between 40% (ie, for areas with the more exophilic and zoophilic vector *A arabiensis*) and 50% (ie, for areas with the more endophilic and anthropophilic vectors *A funestus* and *A gambiae* sensu stricto). In areas of higher transmission, where scale-up of long-lasting insecticide-treated nets alone was insufficient to reach the target, seasonal malaria chemoprevention was generally more resource-efficient than was indoor residual spraying and, hence, was the second intervention to be included (figure 2A). However, in areas with less seasonality in transmission or where vectors were highly indoor resting, indoor residual spraying entered the

most efficient package once moderate levels of coverage of seasonal malaria chemoprevention were achieved (figure 2A). Sensitivity analyses of these optimum packages showed that findings were robust to parameter uncertainty in the natural history of infection, intervention effectiveness parameters, costs of the intervention, and the assumed level of treatment coverage (appendix pp 19–23). After translation of these findings to the epidemiological strata within Africa, in most settings, either long-lasting insecticide-treated nets alone or nets in combination with seasonal malaria chemoprevention were the most resource-efficient intervention packages to achieve a 75% reduction in disease over a 5-year time horizon (figure 3A).

By contrast, when the goal was to reduce transmission to pre-elimination levels (less than one case per 1000 population per year), indoor residual spraying generally replaced seasonal malaria chemoprevention as the more effective second intervention in an optimum package (figure 2B), a finding that was similarly robust to parameter uncertainty (appendix pp 19–23). However, in simulations with 90% coverage of all three interventions, pre-elimination status could be achieved in just 48·6% (95% CI 44·5–52·8) of areas in mainland Africa, representing 43·4% (40·0–49·0) of the population at risk (figure 3B).

Inclusion of intensive mass drug administration (90% coverage at every round) within intervention packages increased the proportion of the population in whom pre-elimination was achievable to 74·9% (95% CI 72·3–81·3) with one round of treatment per year, 81·6% (81·3–88·4) after two rounds per year, and 91·4% (85·2–93·2) with three rounds per year (figure 3D). For mass screen and treatment, the equivalent percentages were 56·5% (54·0–64·8), 63·8% (58·7–70·4), and 81·4% (73·0–89·8; figure 3C). When included in the overall package of interventions needed to achieve the pre-elimination target, mass drug administration was usually added as the second intervention after long-lasting insecticide-treated nets in areas with more outdoor-resting mosquitos. In areas with highly indoor-resting mosquitoes, mass drug administration was generally the third most incrementally cost-efficient intervention (after

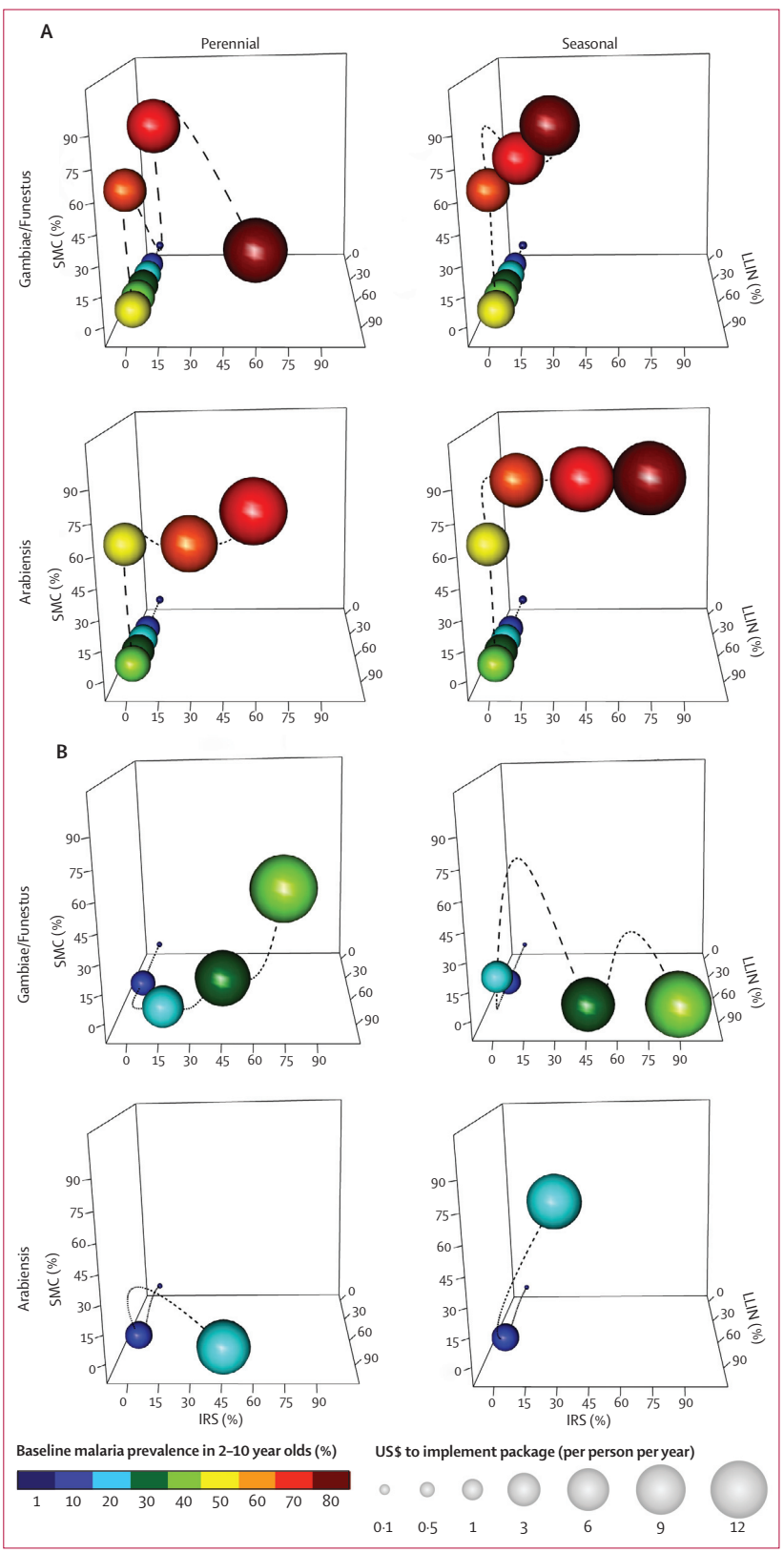

Figure 2: **Optimum packages of currently available malaria control methods**
In every three-dimensional figure, the wire frame plots the percentage of the at-risk population covered with the three interventions within the optimum intervention package, with increasing baseline prevalence. The spheres are colour-coded to reflect the baseline prevalence in every scenario and are sized proportionally to the resources needed to implement the package (US$ at 2012 levels). Missing spheres denote that no sampled package achieved the given target within the required timeframe. LLIN=long-lasting insecticide-treated nets. IRS=indoor residual spraying. SMC=seasonal malaria chemoprevention. (A) Optimum packages to reduce clinical disease by 75% within 5 years after implementation, from a 2000 baseline with different seasonality profiles and vector profiles. (B) Equivalent figure with a target of achieving pre-elimination levels of transmission (less than one case per 1000 population per year) within 20 years after implementation.

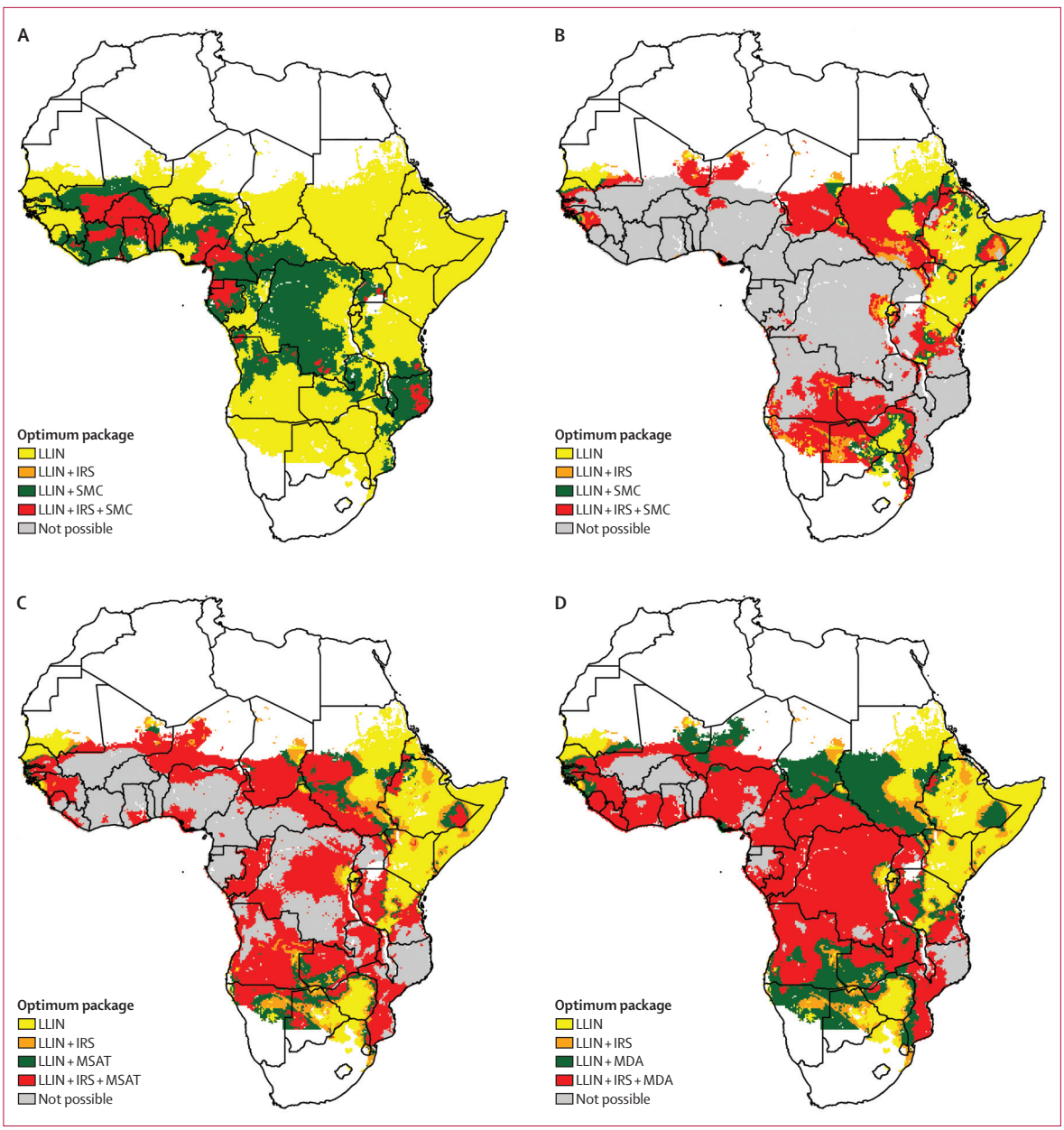

Figure 3: **Optimum packages with different drug-based strategies**
IRS=indoor residual spraying. LLIN=long-lasting insecticide-treated nets. MDA=mass drug administration. MSAT=mass screen and treatment. SMC=seasonal malaria chemoprevention. (A) Optimum package within each 5 km² pixel to reduce clinical incidence by 75% within 5 years from year 2000 levels, with combinations of LLIN, IRS, and SMC. (B) Optimum package within each 5 km² pixel to achieve pre-elimination levels of transmission (less than one case per 1000 per person per year) within 20 years, with combinations of LLIN, IRS, and SMC. (C) Optimum package within each 5 km² pixel to achieve pre-elimination levels of transmission (less than one case per 1000 per person per year) within 20 years, with one, two, or three rounds per year of MSAT instead of SMC, at 90% coverage. (D) Optimum package within each 5 km² pixel to achieve pre-elimination levels of transmission (less than one case per 1000 per person per year) within 20 years, with MDA replacing MSAT.

long-lasting insecticide-treated nets and indoor residual spraying). However, because these areas usually have higher transmission intensity, achieving pre-elimination in these settings is predicted to require a combination of all three interventions (figure 3D).

The spatial scale at which elimination milestones are monitored is likely to be important in terms of whether areas achieve targets. Pre-elimination levels of transmission were predicted to be achievable in 90·9% (95% CI 86·9–94·6) of mainland Africa under a package of long-lasting insecticide-treated nets, indoor residual spraying, and three rounds of mass drug administration per year when assessed at the 5 km² pixel level. However, when assessed at a national level, only 26 (95% CI 22–29)

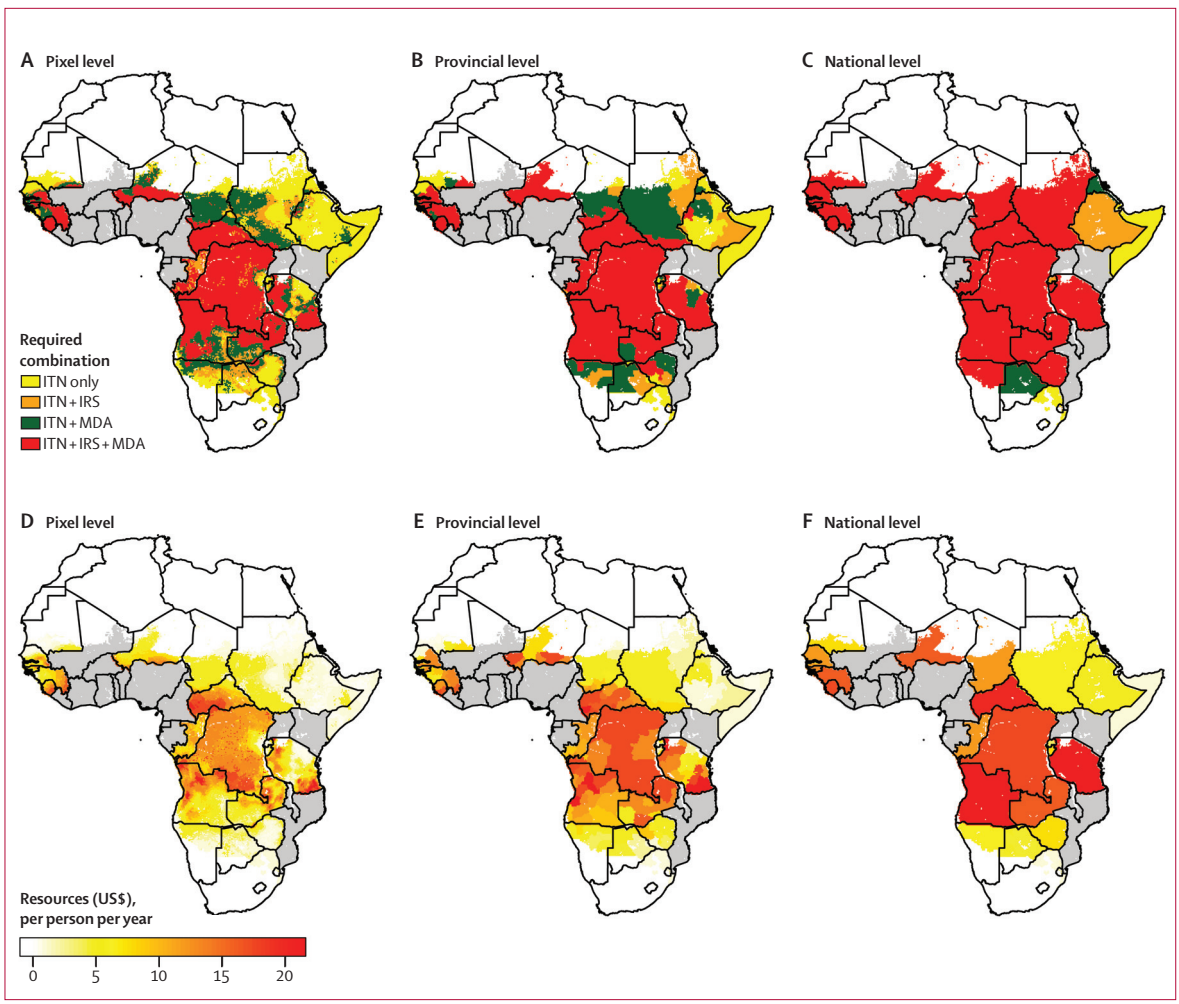

Figure 4: **Optimum combinations of interventions and minimum resources needed to achieve pre-elimination status across Africa**
IRS=indoor residual spraying. ITN=insecticide-treated nets. MDA=mass drug administration. Upper maps show packages when policies are optimised at (A) pixel, (B) provincial, and (C) national levels. Lower maps show the resources needed to implement these packages at (D) pixel, (E) provincial, and (F) national levels.

of 41 countries were predicted to achieve pre-elimination status, representing just 72·3% (95% CI 45·0–79·4) of the total area of Africa and 50·5% (32·9–73·7) of its population. Furthermore, some countries can achieve the pre-elimination threshold even when pockets of higher transmission remain. However, if the target needs to be achieved uniformly across the country, then the task of achieving pre-elimination is substantially harder, with only 22 (95% CI 20–25) countries achieving pre-elimination in all subnational first administrative units (provincial level) in any of our scenarios, and only 20 (18–22) countries achieving the goal across 5 km² pixels.

Within the 26 countries in which we estimated pre-elimination to be achievable at the national level with a package of long-lasting insecticide-treated nets, indoor residual spraying, and three rounds of mass drug administration per year, we estimated that policies optimised at the provincial level would lead to a median 40·6% (IQR 18·5–52·5) per country reduction in resources needed to achieve pre-elimination, relative to a country-wide strategy (figure 4; table 2). For interventions implemented at a 5 km² pixel resolution, the median reduction was 59·4% (40·1–66·4). In countries where pre-elimination might be possible using these tools, the total cost of provincial policies was estimated to be 32·1% (IQR 29·6–34·5) lower than the cost for countries adopting optimum country-level policies (table 2), which is 60·1% (56·9–62·5) of the total savings theoretically achievable by optimising policies at the pixel level. Within individual countries, median provincial level savings were 72% (IQR 51–83) of those at the pixel level. Most cost savings obtained by tailoring control policies at the pixel level are achievable by optimising policies at the provincial scale. Exceptions are countries that have very large provinces (eg, DR Congo) or that have substantial transmission heterogeneity within provinces (eg, Zambia).

	Cost of national policy (US$)	Saving with provincial policy (US$)*	Saving with provincial policy relative to national policy (%)	Further saving with pixel-level policy (US$)†	Saving with pixel-level policy relative to national policy (%)
Angola	25·7 (15·5–35·0)	9·5 (5·7–13·8)	37·5% (34·1–44·8)	5·7 (3·4–7·8)	59·8% (57·2–65·2)
Benin	NP	NP	NP	NP	NP
Botswana	5·0 (3·3–7·0)	1·1 (0·6–2·0)	23·9% (14·6–30·9)	2·1 (1·2–3·1)	64·1% (52·0–70·7)
Burkina Faso	NP	NP	NP	NP	NP
Burundi	10·8 (6·9–14·4)	6·6 (3·9–8·7)	59·1% (54·3–64·7)	0·6 (0·4–1·1)	65·8% (60·8–70·9)
Cameroon	NP	NP	NP	NP	NP
Central African Republic	23·7 (14·6–32·7)	3·6 (2·3–6·8)	16·4% (12·0–23·8)	1·4 (0·8–1·9)	22·2% (18·6–29·8)
Congo (Brazzaville)	13·2 (8·4–18·2)	1·3 (0·5–2·1)	10·9% (4·4–13·2)	3·4 (2·1–4·9)	34·4% (31·0–39·5)
Côte D'Ivoire	NP	NP	NP	NP	NP
Chad	14·2 (8·9–18·8)	5·9 (3·4–8·6)	42·4% (34·6–48·1)	1·6 (1·0–2·3)	53·6% (45·0–60·5)
Djibouti	0·8 (0·6–1·3)	0·4 (0·3–0·8)	53·5% (45·8–59·1)	0·0 (0·0–0·0)	53·5% (45·8–59·1)
DR Congo	20·9 (12·7–27·5)	2·4 (1·4–3·3)	11·6% (10·4–13·6)	5·2 (3·0–7·0)	36·1% (33·6–41·5)
Equatorial Guinea	NP	NP	NP	NP	NP
Eritrea	5·0 (3·7–7·6)	3·0 (2·0–4·9)	61·4% (48·8–68·1)	0·2 (0·0–0·5)	65·1% (50·5–72·5)
Ethiopia	5·1 (3·8–7·7)	2·5 (1·5–4·1)	49·6% (36·5–57·8)	1·5 (1·1–2·2)	79·0% (66·4–85·4)
Gabon	NP	NP	NP	NP	NP
Ghana	NP	NP	NP	NP	NP
Guinea	19·4 (11·6–25·6)	7·6 (4·4–9·9)	38·8% (36·9–41·4)	2·7 (1·6–3·5)	52·6% (50·0–57·0)
Guinea-Bissau	16·0 (10·0–21·1)	7·1 (4·4–9·9)	45·0% (41·6–50·5)	3·4 (2·1–4·5)	66·4% (62·9–69·8)
Kenya	NP	NP	NP	NP	NP
Liberia	NP	NP	NP	NP	NP
Malawi	NP	NP	NP	NP	NP
Mali	NP	NP	NP	NP	NP
Mauritania	9·2 (5·9–12·4)	6·9 (4·1–9·2)	73·6% (69·3–76·5)	0·6 (0·4–0·9)	80·4% (75·7–82·3)
Mozambique	NP	NP	NP	NP	NP
Namibia	9·0 (5·9–12·4)	3·3 (2·0–4·6)	36·1% (29·8–41·8)	0·9 (0·6–1·4)	46·2% (41·0–51·7)
Niger	19·4 (11·6–25·6)	2·4 (1·4–4·1)	13·1% (9·7–19·6)	4·8 (2·8–6·4)	38·1% (35·4–41·9)
Nigeria	NP	NP	NP	NP	NP
Rwanda	5·0 (3·3–7·0)	3·1 (1·7–4·8)	61·3% (52·2–68·3)	0·6 (0·5–1·0)	75·0% (64·2–81·2)
Senegal	14·2 (8·9–18·8)	9·0 (5·5–12·3)	64·3% (60·6–66·4)	2·1 (1·2–2·8)	78·8% (74·8–81·2)
Sierra Leone	20·9 (12·7–27·5)	5·0 (2·9–6·6)	23·4% (22·1–24·7)	1·9 (1·1–2·9)	32·4% (30·7–36·7)
Somalia	1·0 (0·7–1·6)	0·0 (0·0–0·1)	5·1% (1·1–7·7)	0·1 (0·1–0·3)	17·7% (11·8–22·8)
South Africa	4·3 (2·6–5·8)	2·8 (1·5–4·2)	66·9% (53·5–73·1)	0·0 (0·0–0·1)	67·3% (55·4–73·1)
Sudan (including South Sudan)‡	7·2 (5·0–10·1)	3·2 (2·0–4·5)	42·9% (39·5–48·0)	1·1 (0·8–1·8)	60·2% (55·1–62·6)
Swaziland	4·3 (2·6–5·8)	0·8 (0·4–1·3)	16·6% (10·1–22·3)	0·1 (0·0–0·3)	19·4% (14·4–26·2)
Tanzania	25·7 (15·5–35·0)	11·4 (6·8–15·7)	44·3% (42·3–48·0)	5·6 (3·2–7·4)	66·4% (62·7–69·9)
The Gambia	7·2 (5·0–10·1)	2·0 (1·2–3·5)	27·9% (23·3–36·3)	2·1 (1·2–3·1)	58·4% (46·4–62·5)
Togo	NP	NP	NP	NP	NP
Uganda	NP	NP	NP	NP	NP
Zambia	19·4 (11·6–25·6)	3·2 (1·9–4·5)	16·9% (15·6–20·1)	8·1 (4·7–10·5)	59·0% (54·8–62·1)
Zimbabwe	8·8 (5·5–11·7)	3·9 (2·3–5·4)	43·6% (39·1–49·7)	2·8 (1·8–4·3)	77·7% (71·5–81·3)
Median (IQR)	10·0 (5·0–19·4)	3·2 (2·4–6·4)	40·6% (18·5–52·5)	1·8 (0·6–3·25)	59·4% (40·1–66·4)
Total§	14·3 (8·9–19·3)	4·5 (2·7–6·5)	32·1% (29·6–34·5)	3·1 (1·9–4·3)	53·4% (51·2–55·7)

Data are median (IQR) US$ in 2012, unless otherwise stated. Resources needed are assessed at the national level within mainland African countries with endemic malaria, with control policies stratified at different spatial scales. Variation in unit costs of delivering interventions between countries is not shown. NP=not possible to achieve pre-elimination levels of transmission in the country with any simulation. *Difference in cost between policies optimised at the country and provincial level. †Difference in cost between policies optimised at the provincial and pixel level. ‡Country boundaries are as of 2010. §Estimates weighted by population size in each country achieving pre-elimination.

***Table 2*: Estimated resources needed to achieve pre-elimination status, per person at risk per year**

Table 2 shows that there is considerable heterogeneity between countries in the benefits to be gained from more fine-grained policies. Countries with areas of both very high and very low transmission (eg, Tanzania, Angola, Senegal, and Guinea) would save most from moving from a national-level to a provincial-level strategy.

Countries with lower transmission but that still show high degrees of heterogeneity (eg, Mauritania, Zimbabwe, and Ethiopia) are also predicted to achieve very high proportional reductions with such a shift. By contrast, in countries where most of the population live in areas of high transmission (eg, Central African Republic, DR Congo, and Sierra Leone), the necessary resources to achieve elimination are likely to be high irrespective of the spatial scale at which interventions are deployed.

Discussion

In this analysis, we combined dynamic models of the effect of malaria interventions with data for the resources needed to deploy them, to investigate how interventions can be optimised to achieve the various malaria control milestones necessary to achieve elimination. Our results serve to reiterate that universal coverage of long-lasting insecticide-treated nets should be a mainstay of any malaria control policy in Africa because it is the most cost-efficient intervention to reduce both burden and transmission, irrespective of the ecology within a setting.

Our findings show that seasonal malaria chemoprevention is likely to be a more cost-efficient means to reduce the clinical burden of malaria than is additional vector control in the form of indoor residual spraying, particularly in the highly seasonal settings in which it is currently recommended. Although not explicitly modelled, it seems highly plausible that other relatively low-cost, targeted strategies—eg, intermittent preventive treatment in infants and pregnant women—might also be part of an optimum package to reduce burden. However, because these interventions only reach a small proportion of the infectious reservoir,[32] they are unlikely to reduce transmission substantially and, hence, increase the proportion of Africa in which elimination is achievable. By contrast, the addition of indoor residual spraying can allow additional areas to achieve elimination, particularly those in which vector behaviour is susceptible to indoor spraying—ie, where vectors are endophilic. We do not account for secular trends likely to affect transmission over the next 20 years—eg, improvements in housing, urbanisation, and climatic changes. However, our finding that transmission cannot be driven below pre-elimination levels in more than half of Africa, even with 90% coverage, highlights that additional interventions will be necessary in many areas if elimination is ever likely to be feasible.

Our results show that mass drug administration is always strictly superior to mass screen and treatment if implemented at the same coverage level, for several reasons. First, in all but the lowest transmission settings, mass screen and treatment is a more expensive intervention, because of the need to pay for both the drug and the diagnostic. Second, some infections are missed with mass screen and treatment because of imperfect sensitivity of the diagnostic used for screening.[33] Finally, mass drug administration provides additionally a period of prophylaxis for uninfected individuals who receive the drug.[34]

By tackling the asymptomatic and undetectable reservoir of infection, our findings show that mass drug administration could prove a valuable intervention to push more settings closer to elimination. However, such a strategy is likely to be highly resource intensive to maintain at a country level, particularly in higher transmission settings where multiple rounds of treatment per year are likely to be needed to achieve elimination goals. However, we noted that well calibrated, locally tailored policies could reduce substantially the areas and population in which such intensive measures are needed while achieving the same overall level of reduction in transmission. This tailoring has the additional benefit that the financial costs associated with such an intervention, and concerns around drug resistance with wide-scale mass drug administration, could be reduced greatly. The lower resources needed to achieve pre-elimination when interventions were targeted at 5 km² pixel resolution support the notion that such policies should operate as locally as is operationally feasible, particularly as elimination is approached and transmission becomes increasingly heterogeneous. At this stage, importation (which is not captured in our analysis) will become increasingly important. However, relative to a country-level policy to achieve pre-elimination, our findings show that most cost savings achieved when optimising policies at such a high spatial resolution can be achieved at the subnational first administrative (provincial) level. This result suggests that large gains in allocative efficiency are likely to be achievable through strengthening malaria surveillance in most settings, not just those with the resources to operate at very fine spatial scales. These high potential returns on investment support the emphasis placed on ensuring malaria surveillance becomes a core intervention within malaria programmes, as outlined in the WHO Global Technical Strategy for malaria.[12]

In our analysis, we did not include variable first-line treatment rates within our optimum packages; instead, we included high treatment rates within all of our simulations. This rate was fixed partly because we judged adequate care for those with disease a prerequisite to any successful malaria control campaign but also because we did not have adequate data to calculate the resources needed to increase health-care capacity and attendance. However, since rigorous surveillance is likely to be a core focus of programme reorientation towards achieving and sustaining elimination,[28] understanding these constraints will be fundamental to achieving further insight into where elimination is achievable.

Although we did sensitivity analyses, which take into account our uncertainty in the natural history of infection and key variables determining intervention effectiveness, uncertainties remain in some of the other underlying model parameters. For example, the spatial

variation in vector abundance and their associated bionomics remain patchy but are important determinants of the effect of vector control. Also important to note is that, because of scant empirical data, our estimates of the resources needed to deliver interventions do not capture economies of scale and scope, which can reduce costs when policies are widely deployed. Similarly, they do not encompass potential increases in costs associated with achieving very high coverage levels (eg, in targeting hard-to-reach populations) nor those associated with sustaining high coverage over time, especially in the context of transmission and the burden of disease falling to low levels. However, the framework we developed is sufficiently flexible for these factors to be incorporated with little additional computational expenditure if such effects can be quantified adequately.

Our analysis suggests that elimination of malaria in many countries in Africa is unlikely to be possible even with 90% coverage of all currently recommended interventions (and with the option of three rounds of mass drug administration per year). This inability is especially sobering in view of the many other potential obstacles to malaria elimination—eg, development of resistance to drugs and insecticides[35,36] and reported shifts in vector species distributions and behaviour.[37,38] Hence, our results show that sustained investment in the development of new, more effective, malaria control interventions is vital if the goal of malaria elimination across Africa is to be realised. Nevertheless, the costs of deploying such additional strategies could be mitigated substantially by carefully assessed, subnational control strategies informed by the ecology of transmission at the local level.

Contributors

PGTW, JTG, NMF, and ACG had the idea for the study, designed the analysis, and wrote the final report. PGTW did the literature search. PGTW and JTG prepared and did the analysis.

Declaration of interests

PGTW, JTG, ACG, and NMF report grants from the UK Medical Research Council (MRC), during the conduct of the study. JTG also reports grants from the Malaria Vaccine Initiative, outside the submitted work. ACG also reports grants from the Bill & Melinda Gates Foundation, during the conduct of the study; grants from the US National Institutes of Health (NIH), the Wellcome Trust, the Malaria Vaccine Initiative, Medicines for Malaria Venture, Integrated Vector Control Consortium, and WHO, outside the submitted work; non-financial support from GlaxoSmithKline, outside the submitted work; and personal fees from Oxford Policy Management/the Department for International Development and The Global Fund, outside the submitted work. NMF also reports grants from the National Institute of General Medical Sciences, the Bill & Melinda Gates Foundation, and the UK National Institute of Health Research, during the conduct of the study.

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